

# Neuromodulation from electrical current toward myocardial metabolsm.

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The last decade interventional cardiology underwent major progress by the implementation of new flexibel catheters, balloons with superior profiles and improved stent delivery systems. At present, complex angioplasty procedures are possible through the radial, brachial or femoral artery. In addition, thoracic surgeons are able to perform arterial bypass surgery through a small anterolateral incision without the support of a heart lung machine in high risk patients. One of the best clinical examples of the improved cardiovascular therapeutic technology are the hybrid procedures in which severely ill and high risk patients are revascularized by safer and durable combined surgical and angioplasty procedures. Although, these developments in revascularization strategies has improved diagnostic and therapeutical measures, there remains a group of patients, which are no candidates for these revascularization techniques. These patients have end stage coronary artery disease and intractable angina pectoris. A second group with intractable angina pectoris are patients with cardiac syndrome X: typical angina pectoris, normal coronary arteries and often objective signs of myocardial ischemia. A third group with refractory angina pectoris has significant narrowings in arteries < 3 mm. This group is mostly rejected by the surgeon because of the small jeopardized myocardial area. Moreover, the small vessels are prone for restenosis and repeated angioplasty procedures. The conventional antianginal drug treatment such as betablockers, long acting nitrates or calcium channel blockers have been insufficient to ameliorate the intractable angina pectoris. These patients cause an increased economic burden on the total health costs by repeated hospital admissions. In addition, concommitant psychological stress for the patient, his family and physician may lead to further social isolation. Therefore, effective and safe adjuvant treatment strategies were invented to treat intractable angina pectoris in patients with end stage coronary artery. Currently, the most applied clinical adjuvant therapies are chronic intermittent urokinase therapy, transmyocardial laser revascularization and electrical neurostimulation.

Neurostimulation was already used in ancient history. The electrical current from the tail of the electric eel applied to painful arthosis. In 1967 Melzack and Wall treated the first patient with angina pectoris by neurostimulation. They proposed that the mechanism of action could be explained by the 'Gate control theory' which assumes that activation of large non-nociceptive fibres inhibits impuls transmission through small nociceptive fibres. Neurostimulation can be applied internally (spinal cord stimulation, SCS) and externally (transcutaneous electrical nerve stimulation, TENS)

Observational and randomized studies demonstrated that neurostimulation has an antianginal and anti-ischemic effect. To unravel the mechanism of action, a direct effect on the coronary vasculature was measured invasively and noninvasively. The available clinical evidence suggests that the autonomic nervous system is involved by a sympathicolytic mechanism. In a prospective study patients were assigned to either a study group (precordial actual TENS, n=10) or a control group (precordial simulated TENS, n=5, and actual TENS on the back, n=3). Participants were to receive elective angioplasty and had significant disease of the left anterior descending coronary artery in association with New York Heart Association class III angina pectoris. Volumetric flow was simultaneously measured in both branches of the left coronary artery (the left anterior descending and circumflex arteries) at baseline and after 5 minutes of TENS. Coronary volumetric flow was significantly increased in the nonstenotic artery and reduced in the stenotic artery. The total volumetric flow remained unchanged ("reverse steal"). This effect was observed

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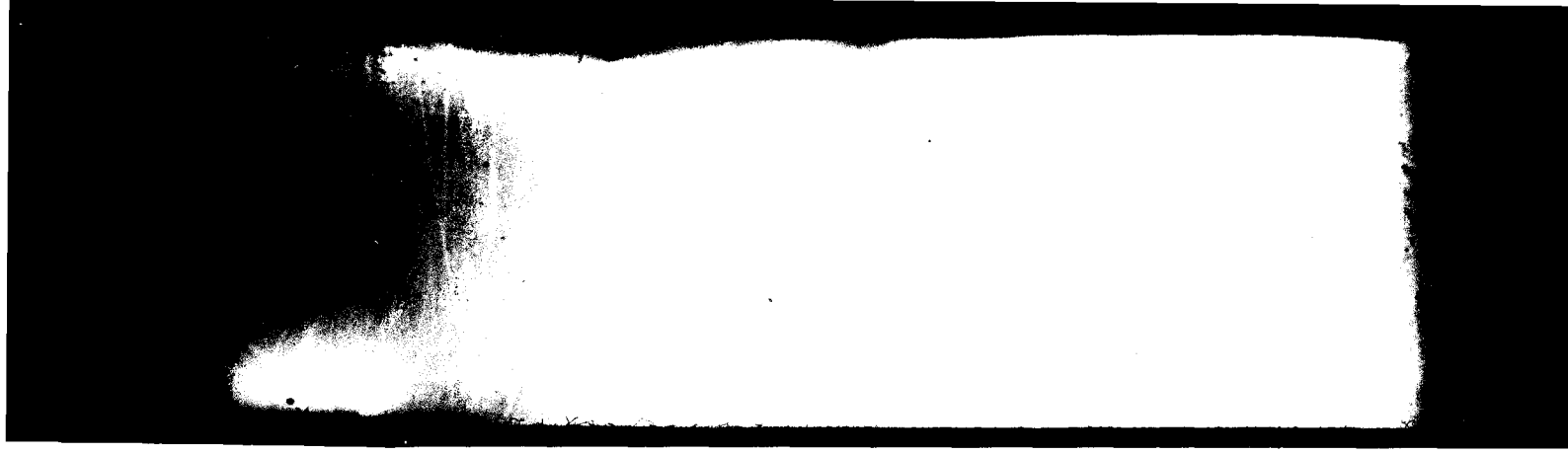



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in the absence of pain or manifest ischemia. In a prior study a "steal" phenomenon ("Robin Hood effect") was observed at the myocardial level from the nonischemic to the ischemic region in patients with end stage coronary artery disease. These findings suggest that neurostimulation induces a cascade of events which results in an improvement of the microcollateral circulation probably as a consequence of a reduced coronary vascular resistance.

To support this hypothesis 8 patients with cardiac syndrome X were treated with TENS. These subjects have a heterogeneous increased rest perfusion caused by a patchily distributed inappropriate sympathetically mediated constriction of prearteriolar vessels. All patients were unresponsive to antianginal drug therapy and did not suffer from esophageal motility disorder. A positron emission tomography (PET) scan was performed at baseline and after 4 weeks of TENS. The coefficient of variation, a measure for myocardial perfusion heterogeneity, was significantly reduced. Rest perfusion was reduced and there was a normal increase of myocardial perfusion during the cold pressor test compared to baseline. This result suggests that myocardial oxygen consumption is reduced. The dynamic changes of the coronary circulation were found in association with a trend to a reduction of the coronary vascular resistance. In a prior PET study, neurostimulation caused cerebral perfusion changes in the same areas involved during cardiac nociception and cardiovascular control. Therefore, neurostimulation has a central and peripheral mechanism of action. The peripheral effect increases myocardial oxygen supply at the one hand and decreases myocardial oxygen demand on the other hand.

To study the long-term clinical efficacy and safety of neurostimulation quality of life was assessed in 26 patients with intractable angina treated by electrical neuromodulation and compared with reference values of healthy subects at baseline, after 3 months and one year follow-up. The clinical efficacy of neurostimulation had significant concomittant improvement of pain and health aspects after 3 months. In addition, following one year social, mental and physical aspects of the quality of life improved. Although, neurostimulation has estimated high daily costs, the subsequent clinical course will maintain the total costs between acceptable ranges. In 24 patients a potential short and long term rebound phenomenon after withholding chronic stimulation was studied. In a random design this study showed that cessation of chronic neurostimulation for severe angina pectoris is safe because it does not result in a reactive increase of angina pectoris or myocardial ischemia. Moreover, in a retrospective single and multicenter long term follow-up study, neurostimulation had no adverse effect on the morbidity and mortality. The mortality of patients treated with neurostimulation is comparable to the mortality of subjects with stable angina pectoris and ranges between 6 to 8 %. This percentage is lower than the 10 % which is reported for patients treated by laser myocardial revascularization. The prognostic variables during treatment with neurostimulation are similar to the conventional risk factors for coronary artery disease such as high age, prior myocardial infarction and diabetes mellitus.

In conclusion, at present electrical neuromodulation is the only effective and safe primary or adjuvant treatment strategy for patients with intractable angina pectoris.